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EXAMINER

GIBBS, TERRA C

ART UNIT PAPER NUMBER

1635

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/003,354

**Applicant(s)**

BENNETT ET AL.

**Examiner**

Terra C. Gibbs

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-10 and 12-15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-10 and 12-15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date May 5, 2003.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☒ Other: Sequence search alignment.

### **DETAILED ACTION**

Pursuant to Applicants Appeal Brief filed September 16, 2003, and the Examiner's reconsideration of the claims, prosecution is reopened on the instant application. The Examiner has reconsidered the claims in light of a new method of searching oligonucleotide sequences performed at the Patent and Trademark Office. This new method of searching was not available during the previous prosecution of the instant application. Any new art now cited was uncovered using this new searching method.

#### ***Response to Amendment***

Applicants Appeal Brief filed September 16, 2004 is acknowledged.

Applicants argue the outstanding 35 U.S.C. 103(a) rejection against claims 1, 2, 4-10, and 12-15 as being unpatentable over Honda et al. (Cell, 1999 Vol. 99: 521-532) Loijens et al. (Journal of Biological Chemistry, 1996 Vol. 271:32937-32942), in further view of Weintraub (Scientific American, 1990 pages 40-46) Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is withdrawn** in view of Applicants arguments. Specifically, the Examiner agrees with Applicants arguments that the prior art combination cited fail to provide motivation to render the instant invention obvious.

#### ***Information Disclosure Statement***

The Information Disclosure Statement filed May 5, 2003 is acknowledged. The references referred to therein have been considered by the Examiner.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$ .

The instant specification teaches a single 5'-untranslated region, coding region, stop codon region, and 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3) (see Table 1). Given their broadest reasonable interpretations, the instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop

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codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$ , which could necessarily imply multiple regions. Applicants have not described multiple 5'-untranslated region, coding region, stop codon region, and 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3). The application as filed only teaches a single 5'-untranslated region, coding region, stop codon region, and 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3). Replacement with the language, a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of the 5'-untranslated region, nucleobases 458 through 2045 of the coding region, nucleobases 2050 through 2069 of the stop codon region, or nucleobases 2063 through 3659 of the 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  would overcome the instant rejection.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

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has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. [U.S. Patent No. 6,190,869].

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$ . Claims 2, 4-10, 12, and 10 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; and wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 12-14 are dependent are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein the compound of claim 1 further comprises a pharmaceutically acceptable carrier or diluent and colloidal dispersion system. Claim 15 is drawn to a method of inhibiting the

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expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  in cells or tissues *in vitro* with the compound of claim 1 so that the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  is inhibited.

Bennett et al. disclose a modified antisense oligonucleotide targeted to protein kinase C-theta with the following sequence: 5'-cctgacaagactggcaggac-3' (see SEQ ID NO:15). Bennett et al. further disclose that the antisense oligonucleotide targeted protein kinase C-theta was effective *in vitro* (see Table 1). This antisense oligonucleotide is reverse complementary to bases 3272-3290 of the 3'-untranslated region of a nucleic acid encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3) of the instant invention. It is noted that the reverse complementarity between the antisense oligonucleotide targeted to protein kinase C-theta disclosed by Bennett et al. and nucleobases 3272-3290 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to protein kinase C-theta disclosed by Bennett et al. exhibits almost 90% local similarity to nucleobases 3272-3290 of SEQ ID NO:3 of the instant invention, as it contains two mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to protein kinase C-theta disclosed by Bennett et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  as defined in the instant specification at page 14, lines 17-25. Accordingly, the antisense oligonucleotide disclosed by Bennett et al. would specifically hybridize to bases 3272-3290 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions falls to Applicant. See MPEP

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2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the modified antisense oligonucleotide disclosed by Bennett et al. would or would not have the additional functional limitation of "inhibiting expression" of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 4-10, and 12-15 are anticipated by Bennett et al.

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. [U.S. Patent No. 6,303,374].

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Zhang et al. disclose a modified antisense oligonucleotide targeted to caspase 3 with the following sequence: 5'-aagttgtatttcatatgtt-3' (see SEQ ID NO:78). Zhang et al. further disclose that the antisense oligonucleotide targeted caspase 3 was effective *in vitro* (see Table 1). This antisense oligonucleotide is reverse complementary to bases 586-605 of the coding region of a nucleic acid encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3) of the instant invention. It is noted that the reverse complementarity between the antisense oligonucleotide targeted to caspase disclosed by Zhang et al. and nucleobases 586-605 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to caspase 3 disclosed by Zhang et al. exhibits 85% local similarity to nucleobases 586-605 of SEQ ID NO:3 of the instant invention, as it contains three mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to caspase 3 disclosed by Zhang et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  as defined in the instant specification at page 14, lines 17-25. Accordingly, the antisense oligonucleotide disclosed by Zhang et al. would specifically hybridize to bases 586-605 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for

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believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” In *re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In *re Best*, 562 F.2d at 1255, 195 USPQ at 433.” See also MPEP 2112: “[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product.” The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the modified antisense oligonucleotide disclosed by Zhang et al. would or would not have the additional functional limitation of “inhibiting expression” of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 4-10, and 12-15 are anticipated by Zhang et al.

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wyatt et al. [U.S. Patent No. 6,440,738].

Wyatt et al. disclose a modified antisense oligonucleotide targeted to casein kinase 2-beta with the following sequence: 5'-gtcacgaaggcccgaggag-3' (see SEQ ID NO:38). Wyatt et al. further disclose that the antisense oligonucleotide targeted casein kinase 2-beta was effective *in vitro* (see Table 1). This antisense oligonucleotide is reverse complementary to bases 412-428 of the 5'-untranslated region of a nucleic acid encoding phosphatidylinositol-4-phosphate 5-kinase

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I $\alpha$  (SEQ ID NO:3) of the instant invention. It is noted that the reverse complementarity between the antisense oligonucleotide targeted to casein kinase 2-beta disclosed by Wyatt et al. and nucleobases 412-428 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to casein kinase 2-beta disclosed by Wyatt et al. exhibits 94% local similarity to nucleobases 412-428 of SEQ ID NO:3 of the instant invention, as it contains only one mismatch (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to casein kinase 2-beta disclosed by Wyatt et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  as defined in the instant specification at page 14, lines 17-25. Accordingly, the antisense oligonucleotide disclosed by Wyatt et al. would specifically hybridize to bases 412-428 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re*

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Best, 562 F.2d at 1255, 195 USPQ at 433.” See also MPEP 2112: “[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product.” The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the modified antisense oligonucleotide disclosed by Wyatt et al. would or would not have the additional functional limitation of “inhibiting expression” of phosphatidylinositol-4-phosphate 5-kinase  $I\alpha$  under generally any assay conditions.

Therefore, absent evidence to the contrary, claims 1, 2, 4-10, and 12-15 are anticipated by Wyatt et al.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loijens et al. (Journal of Biological Chemistry, 1996 Vol. 271:32937-32942), in view of Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81), Baracchini et al. [U.S. Patent No. 5801154], and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$ . Claims 2 and 4-10 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; and wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 12 and 14 are dependent on claim 1 and include all the limitations of claim 1 with the further limitation comprising an antisense oligonucleotide of claim 1 and a pharmaceutically acceptable carrier or diluent. Claim 15 is drawn to a method of inhibiting the expression of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  in cells or tissues *in vitro* with a compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through

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2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3), wherein said compound specifically hybridizes with said region and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$ .

Loijens et al. teach the cDNA and peptide sequence of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  and the tissue distribution of human phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (see Figures 1 and 3). It is noted that the phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  cDNA sequence taught by Loijens et al. is 100% identical to SEQ ID NO:3 of the instant invention. Loijens et al. do not teach or suggest the use of antisense compounds of any type to target and inhibit the expression of phosphatidylinositol-4-phosphate 5-kinase I $\alpha$ .

Agrawal et al. teach "antisense oligonucleotides have become efficient molecular biological tools to investigate the function of any protein in the cell" (see Abstract). Further, Agrawal et al. teach "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years. In principle, the antisense approach should allow the design of drugs that specifically intervene with the expression of any gene whose sequence is known" (see page 72, first paragraph).

Baracchini et al. teach, "oligonucleotides are designed to bind either directly to mRNA or to a selected DNA portion forming a triple stranded structure, thereby modulating the amount of mRNA made from the gene"... "the relationship between an oligonucleotide and its complementary target nucleic acid is commonly denoted as antisense"... "it is preferred to target specific genes for antisense attack"... (see column 3, lines 17-41). Baracchini et al. further teach

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modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. finally teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19). Baracchini et al. also teach antisense oligonucleotides, 20 nucleobases in length, that can specifically hybridize with a 5'-untranslated sequence, 3' untranslated sequence, or coding sequence (see column 9, lines 6-67 and column 10, lines 1-25 and Table 1) of a gene of interest.

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make antisense nucleic acids targeting phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3) using the sequence taught by Loijens et al., the motivation of Agrawal et al., and following the methods of Baracchini et al. and Fritz et al.

It would have been obvious to make antisense nucleic acids targeting phosphatidylinositol-4-phosphate 5-kinase I $\alpha$  (SEQ ID NO:3) since Loijens et al. taught the

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sequence of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  (SEQ ID NO:3) and Agrawal et al. teach making an antisense oligonucleotide if the mRNA sequence. It would have been further obvious to make antisense nucleic acids targeting phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  (SEQ ID NO:3) because Loijens et al. taught PIP5KI $\alpha$ 2 and PIP5KI $\alpha$ 3 as splice variants of PIP5KI $\alpha$ 1 which permit comparative studies of each isoform. One of ordinary skill in the art would have been motivated to inhibit the expression of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  in an effort to determine the biological function of phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  for drug design as suggested by Agrawal et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making the antisense oligonucleotides 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  (SEQ ID NO:3), since Baracchini et al. taught antisense oligonucleotides, 20 nucleobases in length, targeted to the 5'-untranslated region, coding region, stop codon region, or 3'-untranslated region, that can specifically hybridize with a gene of interest (see column 9, lines 6-67 and column 10, lines 1-25 and Table 1). It is noted that the regions specified in the claims amount to much of the phosphatidylinositol-4-phosphate 5-kinase  $\text{I}\alpha$  full length sequence taught by Loijens et al. Further, one of ordinary skill in the art would have been motivated to make an antisense compounds within that length because it is well known in the art that an antisense oligonucleotide of 8 to 50 nucleobases in length is a conventional size range for optimal binding of a gene of interest and for ease of synthesis and delivery to cells in culture. One of ordinary

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skill in the art would have been motivated and had a reasonable expectation of success in modifying antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

#### ***Response to Arguments***

It is noted that in the Office Action mailed May 1, 2003, 103(a) rejection against claims 1, 2, 4-10, and 12-15 as being unpatentable over Honda et al. (Cell, 1999 Vol. 99: 521-532) Loijens et al. (Journal of Biological Chemistry, 1996 Vol. 271:32937-32942), in further view of Weintraub (Scientific American, 1990 pages 40-46) Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is withdrawn** in view of Applicants arguments. Specifically, the Examiner agrees with Applicants arguments that the prior art combination cited fail to provide motivation to render the instant invention obvious.

However, in light of the new 35 USC 103(a) rejection as presented above, the combination of references renders the instant invention obvious. Therefore invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg

November 10, 2004

JOHN L. LEГУYADER  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

# Applicants Copy Sequence search alignment

AUTHORS  
TITLE  
JOURNAL  
FEATURES  
source

Bennett, C. Frank, and Cowser, L. M.  
Antisense inhibition of protein kinase C-theta expression  
Patent: US 6190869-A 15 20-FEB-2001;  
Location/Qualifiers  
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/organism="unknown"  
/mol\_type="unassigned DNA"

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Best Local Similarity 89.5%; Pred. No. 1.1e+02;  
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Db 19 TCCTGCCAGTCTCTGTCAGG 1

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ACCESSION AR130764  
VERSION AR130764.1 GI:14119089  
KEYWORDS  
SOURCE Unknown.  
ORGANISM Unknown.  
REFERENCE 1 (bases 1 to 20)  
20 bp DNA linear PAT 15-MAY-2001

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DEFINITION      Sequence 38 from patent US 6440738.
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SOURCE          Unknown.
ORGANISM        Unknown.
                Unclassified.
REFERENCE       1 (bases 1 to 20)
AUTHORS         Wyatt,J.
TITLE           Antisense modulation of casein kinase 2-beta expression
JOURNAL         Patent: US 6440738-A 38 27-AUG-2002;
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Db 20 CTCCTCCGGGCCCTTCGT 4

# Applicants Copy Sequence search alignment

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DEFINITION Sequence 78 from patent US 6303374.  
ACCESSION AR172953  
VERSION AR172953.1 GI:17912444  
KEYWORDS  
SOURCE Unknown.  
ORGANISM Unknown.  
Unclassified.  
REFERENCE 1 (bases 1 to 20)  
AUTHORS Zhang, H. and Cowser, L.M.  
TITLE Antisense modulation of caspase 3 expression  
JOURNAL Patent: US 6303374-A 78 16-OCT-2001;  
FEATURES Location/Qualifiers  
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Tue Nov 2 10:07:21 2004

/organism="unknown"  
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Best Local Similarity 85.0%; Pred. No. 1.5e+02;  
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Qy 586 AACATATAAAAAGACAACCT 605  
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Db 20 AACATATGAAAATACAACCT 1